REMARKS

The Office Action of June 4, 2002 presents the examination of claims 1-11. Claims 12-18 are added. Support for claims 12-18 is found in the specification. Particularly, support for claim 12 is found on page 6, lines 21-23 of the specification; support for claim 13 is found on page 6, lines 24-27, support for claim 14 is found on page 6, line 28 to page 7, line 1; support for claim 15 is found on page 7, lines 2-3; support for claim 16 is found on page 7, lines 4-5; support for claim 17 is found on page 7, lines 6-8; and support for claim 18 is found on page 7, lines 9-11. No new matter is inserted into the application.

Specification

The Examiner objects to the specification for the misspelling of "polysorbate" as "polysorvate." In response to the Examiner's remarks, Applicants amend the specification on pages 14, 22, and 26 to correctly recite "polysorbate." Thus, the instant objection is overcome.

Rejection under 35 U.S.C. § 103(a)

Paragraph 3 of the Office Action

The Examiner rejects claims 1-6 and 8-11 under 35 U.S.C. § 103(a) for allegedly being obvious over Fujioka '547 (U.S. Patent 5,851,547) in view of Fujioka '253 (U.S. Patent 4,985,253). Applicants respectfully traverse. Reconsideration of the claims

and withdrawal of the instant rejection are respectfully requested.

The Examiner argues that Fujioka '547 teaches the sustained release preparation of the present invention absent the specific use of polyethylene glycol. Fujioka '253 is relied upon merely to teach the use of polyethylene glycol.

Applicants respectfully disagree with the Examiner's statements. The sustained release preparation of the present invention differs substantially from the drug formulation disclosed in Fujioka '547 as is discussed below, such that the reliance upon Fujioka '253 is irrelevant. The present invention is not obvious to a person skilled in the art from the disclosure of Fujioka '547 and Fujioka '253, and further the effect of the preparation of the invention is not obvious over Fujioka '547 and Fujioka '253.

The drug formulation of Fujioka '547 uses water-soluble drugs (see, e.g., column 4, line 55). In contrast, the sustained release preparation of the invention uses a lipophilic drug. This feature of the present invention is recited in the claims. Lipophilic drugs differ from water-soluble drugs in terms of the process of drug release from a formulation wherein a water-impermeable and biocompatible material, such as silicone, is used as a carrier.

A channeling phenomenon participates in the release mechanism for water-soluble drugs from a water-impermeable and

biocompatible material carriers. The water-soluble drug is released by diffusion through resulting channels, which are continuously formed by the repetition of the process of dissolution of the drug in the ambient water in the vicinity of the surface of the formulation and followed by dissolution of the drug present around the resulting cavities (see, Fujioka '547, column 1, lines 47 to 56). In the process, because of great solubility of the water-soluble drug in water, channel formulation immediately occurs upon penetration of water into the inside of the formulation, and this immediate channel formation drives this process. On the other hand, solubility of lipophilic drugs is poor in water, and therefore, channel formation in the formulation would occur much slower than that in water-soluble drug formulations. Thus, in the drug release mechanism for lipophilic drugs, there is little contribution from channel formation in drug release.

Another process participates in the drug release of a lipophilic drug from the water-impermeable carriers. Here, the lipophilic drug, because of its fat-soluble property, can diffuse through a water-impermeable carrier to migrate to the surface of the formulation and be released (see page 4, lines 23 to 27 of the specification). On the contrary, the water-soluble drug does not dissolve in a water-impermeable material, and therefore, such process does not occur in the drug formulation of water-soluble drugs as disclosed in Fujioka '547.

Thus, those skilled in the art would not anticipate that the lipophilic drug is applicable to a formulation wherein a water-soluble drug is contained in a water impermeable carrier, due to the difference in release process as explained above. Accordingly, those skilled in the art would not be motivated to apply lipophilic drugs to the drug release system as taught in Fujioka '547 directed to water-soluble drugs, and therefore, the sustained release formulation for lipophilic drugs of the present invention is not obvious over Fujioka '547.

Further, the use of polyethylene glycol as taught in Fujioka '253 does not influence the non-obviousness of the claimed invention. Fujioka '253 is merely relied upon to teach the use of polyethylene glycol. Fujioka '253 does not make up for the differences between the drug release process for water-soluble drugs and for lipophilic drugs as discussed above.

Fujioka '547 neither teaches nor suggests that a lipophilic drug and a water-soluble substance are dispersed in a state of solid at the body temperature of an animal or a human being to which the preparation is to be administered. This feature of the present invention is recited in claim 1. Accordingly, the preparation of the invention defined by the claimed construction is not obvious over Fujioka '547, and further, the effects obtained by taking this construction into account is not obvious to those skilled in the art.

The sustained release preparation of the present invention

solves the problem accompanied with sustained release preparations for lipophilic drugs wherein the release of the lipophilic drug from the formulation is slow (see page 5, lines 16 to 25 of the specification). Generally, lipophilic drugs are hard to dissolve in water, which suppresses the drug release from the preparation, and therefore, in some drugs, the release of a sufficiently effective amount of the drug may not be accomplished. However, the sustained release preparation of the invention can enhance release of a lipophilic drug from the preparation (page 4, line 23 to page 5, line 14 of the specification).

The preparation of the invention 1A (symbol ○), which possesses the above construction, can increase surprisingly the release rate of the drug as compared with the control preparation (symbol □), as shown in Figure 3. Moreover, by covering with an outer layer, the preparation of the invention can release a nearly constant amount of the drug for prolonged period at the rate significantly greater than that of the control preparation, as shown in the preparation 1 (symbol ●) of Figure 3.

This effect is based on the process as disclosed on page 7, line 12 to page 8, line 15 of the specification. That is, permeation of the water into inside of the preparation occurs by the water-soluble substances being contained in a state of solid, and thereby, the extend of contact of the lipophilic drug is

enhanced by water-soluble substance dissolved in water infiltrated into the preparation.

Fujioka '547 fails to disclose or suggest these effects and processes of the sustained release preparation of the invention. From the beginning, Fujioka '547 intends a drug formulation for water-soluble drugs, which does not require the construction of the preparation of the invention as defined in the claims. Therefore, the construction of the preparation of the invention is not obvious to those skilled in the art, and of course, the effects obtained by the construction are not obvious to those skilled in the art.

Further, use of polyethylene glycol as taught in Fujioka '253 does not influence the non-obviousness of the claimed invention, in view of the construction of the preparation of the invention which is neither disclosed nor suggested by Fujioka '253.

In summary, the combination of Fujioka '547 and Fujioka '253 fails to render the present invention obvious. Withdrawal of the instant rejection is respectfully requested.

Paragraph 4 of the Office Action

The Examiner also rejects claims 1-3, 5-7, and 11 under 35 U.S.C. § 103(a) for allegedly being obvious over Kannji '581 (JP 07 330 581). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are

respectfully requested.

The implantable sustained release immunosuppressive drug disclosed in Kannji '581 does not have the element defined in claim 1, wherein the lipophilic drug and a water-soluble substance are dispersed, in a solid state at the body temperature of an animal or a human being to which the preparation is to be administered, in a water-impermeable and biocompatible material.

Kannji '581 teaches,

> In an implantable sustained release immunosuppressive drug of the present invention..., the nonionic surfactant added to the bioabsorbable aliphatic polyester forms a matrix containing **the immunosuppressive agent dissolved therein** and thereby **prevents precipitation of the agent** during preparation. Such matrix in which **the agent is homogeneously dissolved** allows...[emphasis added]."

See, page 13, line 13 to page 14, line 2 of the English translation of Kannji '581. Thus, Kannji '581 merely teaches that a drug and a nonionic surfactant are both homogeneously dissolved in a matrix and fails to teach that these ingredients are dispersed in a state of solid.

Moreover, no description or suggestion relevant to that a lipophilic drug and a water-soluble substance are dispersed in a state of solid in a water-impermeable and biocompatible material is found anywhere in Kannji '581. Accordingly, the invention of claims 1-3, 5-7 and 11 is not obvious to those skilled in the art over Kannji '581. Withdrawal of the instant rejection is respectfully requested.

Conclusion

As discussed above, the sustained release preparation of the invention can enhance and control the release rate of the lipophilic drug, as shown in Figure 3 of the specification, by taking the unique construction that the lipophilic drug and a water-soluble substance are dispersed, in a state of solid at the body temperature of an animal or a human being to which the preparation is to be administered. The process considered as the cause of this effect is explained above. This effect of the present invention is absolutely non-obvious to those skilled in the art.

Summary

Applicants respectfully submit that the above amendments and/or remarks fully address and overcome the rejections and objections of record. The instant claims are now in condition for allowance. Early and favorable action by the Examiner is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. 45,702) at the telephone number of the undersigned below.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of one (1) month to October 4, 2002, in which to file a reply to the Office Action.

The required fee of $110.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

The paragraph beginning on page 14, line 18, has been amended as follows:

To a solid comprising a lipophilic drug and a water-soluble substance, a water-impermeable and biocompatible material, or both of the solid comprising the lipophilic drug and the water-soluble substance and the water-impermeable and biocompatible material, an additive such as physiologically acceptable stabilizers, solubilizing agents, preservatives, analgesics may be added. A liquid substance may be also added so long as a lipophilic drug and a water-soluble substance in a drug dispersion keep in a solid shape at the body temperature. A surfactant, typical solubilizing agent, can alter an infiltration rate of water and a solubility of a lipophilic drug at the site where water is infiltrated, and therefore, is useful for altering release of the lipophilic drug from the preparation. Specific examples are [polysorvate] polysorbate 20, [polysorvate] polysorbate 80 and so on.

The paragraph beginning on page 22, line 14, has been amended as follows:

Preparation 1 prepared in Example 1 was allowed to stand in a phosphate buffered solution (containing 0.3% [polysorvate]

polysorbate 20) (1ml) at 37°C, and then, the quantity of ivermectin released from the preparation was determined by a high performance liquid chromatography to obtain an accumulated release rate thereof. The results are shown in Fig. 3.

The paragraph beginning on page 26, line 28, has been amended as follows:

--Ivermectin (700mg), polyethylene glycol 4000 (700 mg) and [polysorvate] polysorbate 20 (7mg) were dissolved in methanol (4ml), dried under nitrogen flow followed by drying in vacuo. The obtained solid was milled and passed through a [sieve(212μm)] sieve (212μm). A portion (600 mg) of the obtained powder mixture and Silastic™ Medical Grade ETR Elastomer Q7-4750 Component A (700mg) and Silastic™ Medical Grade ETR Elastomer Q7-4750 Component B (700mg) were mixed to give a drug dispersion component. Silastic™ Medical Grade ETR Elastomer Q7-4750 Component A (50mg) and Silastic™ Medical Grade ETR Elastomer Q7-4750 Component B (50mg) were mixed to give a coating layer component. Thus obtained drug dispersion component and coating layer component were molded by extruding from a double extruder (1.9mm of the inner diameter of the outer nozzle and 1.6mm of the inner diameter of the inner nozzle) which enables them to be molded by extruding so that the drug dispersion is concentrically coated with the coating [layerwhich] layer which enables them to be molded by extruding so that the drug dispersion is

concentrically coated with a coating layer, and was allowed to stand at room temperature to cure, [and allowed to stand at room temperature to cure,] which was cut to obtain the cylindrical preparation 5 (the length of the preparation is 5mm, the diameter of the preparation is 1.9mm, and the diameter of the drug dispersion is 1.5mm).--

In the claims:

Claims 12-18 are added.